UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/386,680	02/10/95	GROTENDORST G.	FD-4129

EXAMINER	
SPECTOR, L	

ART UNIT	PAPER NUMBER
1812	3

18N2/1011
SPENSLEY HORN JUBAS & LUBITZ
1880 CENTURY PARK EAST
SUITE 500
LOS ANGELES CA 90067

DATE MAILED: 10/11/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 5-13 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-4, 14-28 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 5-13 are rejected.

5. ☑ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

386680.1
9/29/95

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Part III: Detailed Office Action

This application is a divisional of U.S. Patent Number 5,408,040, application Serial No. 08/167628. Claims 5-13 are pending and under consideration.

Applicants are advised that the Examiner has, by informal amendment, amended the cross reference to the parent application to indicate that it issued April 18 1995 as U.S. Patent Number 5,408,040.

Formal Matters:

The application is objected to because of alterations which have not been initialed and/or dated as is required by 37 C.F.R. §§ 1.52(c) and 1.56. A properly executed oath or declaration which complies with 37 C.F.R. § 1.67(a) and identifies the application by serial number and filing date is required. The surcharge set forth in 37 C.F.R. § 1.16(e) is also required if it has not been previously paid in the application.

The alterations in question are the underlining of specific words in the specification as follows: "mitogenic" and "chemotactic" at the last two lines of page 2, "degenerate" at page 5 line 23, and "functionally unchanged" at page 5 line 26.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts, compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. Complete revision of the content of the abstract is required on a separate sheet.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-13 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to nucleic acids which encode the protein of SEQ ID NO:2, in its entirety. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The disclosed uses for the claimed polynucleotides include (a) use for recombinant production of the encoded protein, and (b) use as hybridization probes to obtain homologues or alleles of the particularly disclosed protein. Enablement is not commensurate in scope with claims to any nucleic acid which encodes any protein with CTGF activity or any functional fragment thereof. The specification defines such to include both naturally occurring and mutated forms of the disclosed protein (see page 5, line 20). However, there is no guidance in the specification, other than the disclosure of the sequence of the protein, as to which portions of the protein would be necessary for activity, nor which portions of the protein could be altered or deleted while retaining such activity.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, catalysis and in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions

or no substitutions. However, applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Such a definition might also read on previously characterized proteins, or alternatively, might include proteins with additional functions or activities neither envisioned nor enabled by applicants in the current invention. See Ex parte Forman, 230 U.S.P.Q. 546 (BPAI 1986) with regard to the issue raised above.

It was found in *Ex parte Maizel* (27 USPQ2d 1662 at 1665) that:

> Appellants have not chosen to claim the DNA by what it is but, rather, by what it does, i.e., encoding either a protein exhibiting certain characteristics, *or* a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in *In re Hyatt*, 708F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "biologically functional equivalent thereof" is that it covers any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses, at most, only a specific DNA segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claims."

In the instant case, the claims, which encompass nucleic acids encoding any mutein or fragment of the disclosed protein which retain mitogenic and chemotactic activity, approach the breadth of the claims in *Maizel*, and are similarly unenabled.

Scope

The Examiner recognizes that Applicants may have been the first to identify, clone, and express CTGF. However, the cloning of CTGF should not entitle Applicants to each and every permutation of the DNA sequences. While the Applicants should be entitled to coverage and protection for that which is reasonably due them from the breadth and enablement disclosed in the specification, Applicants should not be entitled to protection for the specific language of the Claims because they have clearly not enabled the scope of such. The Examiner further recognizes that one of ordinary skill in the art would agree that the invention reasonably envisions the full length sequences and sequences that are the result of degeneracy. *as have been*

disclosed. However, the specification does not sufficiently enable any more than the stated DNA sequences above and the language of the Claims should be so limited. Such broad Claims should not be allowed because the instant specification is not enabled for them. The Examiner recognizes that the Applicants seek broad coverage for their Invention, inclusive of minor variations, so that the skilled artisan would not be able to avoid infringement by merely making minor changes and the Examiner is willing to give Applicants sufficiently broad Claims for which there is enablement. However, the Claims are not restrictive to these minor variations, and enablement of such variations in the specification is extremely limited.

With regard to the use of the claimed nucleic acids as hybridization probes, enablement is not commensurate in scope with the claims because the claims are not restricted to fragments of the particularly disclosed nucleic acid sequence, and further, because the specification does not adequately teach which portions of the disclosed nucleic acids would be expected to be functional as hybridization probes (in addition to the issue addressed above regarding lack of identification of which portions of the disclosed nucleic acid encode "functional fragments" of CTGF). The success of using a nucleic acid as a hybridization probe depends upon the probe being specific, that is, not cross-hybridizing with an unacceptable number of undesired sequences. Selection of such a probe requires knowledge as to conserved regions of the nucleic acid, as well as the elimination of regions which are likely to cross-hybridize. The instant specification gives no guidance in the selection of fragments of the disclosed nucleic acid appropriate for hybridization use, and in the absence of such guidance, it would require undue experimentation to determine which of the innumerable possible fragments would be suitable for such use.

Claims 5-13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is indefinite as it is not clear whether "functional fragment thereof" refers to the nucleic acid (in which case it is not clear what a functional fragment is), or alternatively to CTGF

polypeptide.

Claim 8 is indefinite as a single polynucleotide sequence cannot, by definition include all sequences which are degenerate as a result of the genetic code (the claim is drawn to a single sequence which "includes" numerous other sequences). Further, the claim does not appear to further limit the independent claim (5), which already encompasses all such species. A claim to any nucleic acid which encodes a particular protein includes all possible codon degeneracies.

Claim 9 is indefinite for using the plural "vectors". Claims 10 and 11 are indefinite because claim 9 lacks antecedent basis for "the vector" and "a DNA vector".

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 5-12 are rejected under 35 U.S.C. § 102(a) as anticipated by Ryseck et al. (Cell Growth & Differentiation 2:225).

Ryseck et al. disclose cloning and expression of cDNA encoding fisp-12 from NIH 3T3 cells, a protein predicted to have 348 amino acids, with a predicted molecular weight of 37,792 daltons (p. 226, col. 2). The cDNA was in a biologically functional vector, and was used to transform *E. coli* (prokaryotic) cells, see page 226, second column for example. A comparison of the amino acid sequences of fisp-12 and CTGF reveals only 13 discrepancies in the region between residues 86 and 392 (based on the numbering of Seq. ID No: 1, see attachment which demonstrates the sequence alignment). There is greater divergence in the region preceding residue 86. However, Ryseck et al. identify this region as a signal sequence, which would have

no effect on the activity of the protein. At the time of their disclosure, Ryseck et al. were unaware of the function of fisp-12, and made no mention of any ability to bind PDGF receptors. However, the degree of identity between the two proteins is such that the DNA encoding fisp-12 as disclosed by Ryseck et al. is, in the absence of evidence to the contrary, presumed to encode at least a functional fragment of CTGF.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claim 13 is rejected under 35 U.S.C. § 103 as being unpatentable over Ryseck et al. The teachings of Ryseck et al. are discussed above in the rejection of claims 5-12 under 35 U.S.C. §102(a). In addition to the above teachings, Ryseck et al. teach at page 226, second column that the cDNA encodes a protein with a predicted signal sequence with a putative cleavage site at amino acids 25-26. Ryseck et al. neither teaches or suggests transformation of eukaryotic cells with the disclosed cDNA. It would have been obvious to the person of ordinary skill in the art

at the time the invention was made to use the cDNA disclosed by Ryseck et al. to construct a eukaryotic expression vector, and to transfect mammalian host cells with that vector, for the purpose of confirming the proposed signal cleavage site. One of ordinary skill in the art would have been motivated to do so to confirm Ryseck's supposition and positively identify the mature protein, and would have had every expectation of success, as vectors and host cells for expression of genes in mammalian cells are well known in the art and routinely used for their known and expected properties.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Matsuoka et al. disclose the identification and purification of a PDGF-related protein of 34-36 kilodaltons (kD) from human wound fluid. The last paragraph of the first column, p. 4416 indicates that the peptides are biologically active as chemoattractants (e.g. chemotactic) and mitogens for connective tissue cells, and that they crossreact with anti-human PDGF IgG (antibodies).

Campochiaro et al. disclose the isolation of a PDGF-like protein from retinal pigment epithelial cells. Said protein has a relative mobility of 36-38 kD, is mitogenic and chemotactic, and binds to PDGF antibodies.

Shimokado et al. disclose the isolation of a PDGF-like protein of 37 kD, isolated from activated human alveolar and peritoneal macrophages. Said protein is mitogenic for connective tissue cells (p. 278), inhibited by anti-PDGF IgG (p.279) and competes for binding to PDGF receptors (paragraph bridging pages 279-280).

Advisory Information:

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Garnette D. Draper, can be reached at (703)308-4232.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The Art Unit 1812 Fax Center number is (703) 308-0294. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the Examiner at the telephone number above when a fax is being transmitted.

Lorraine Spector

Lorraine Spector, Ph.D.
Patent Examiner

LMS
386680.1
9/28/95